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Hot off the Press

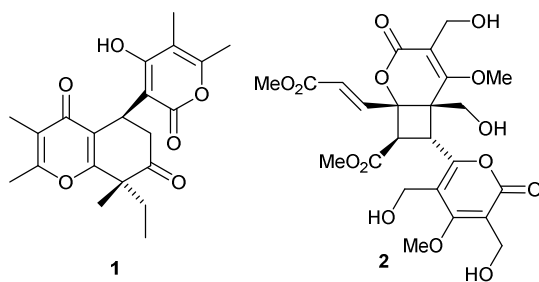
Robert A. Hill and Andrew Sutherland

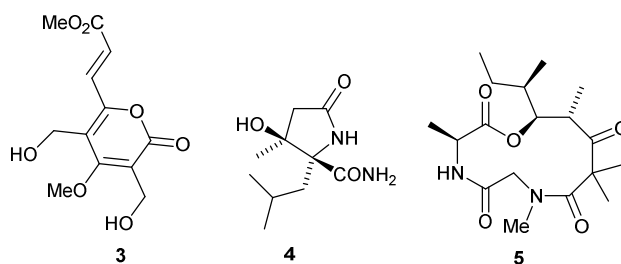
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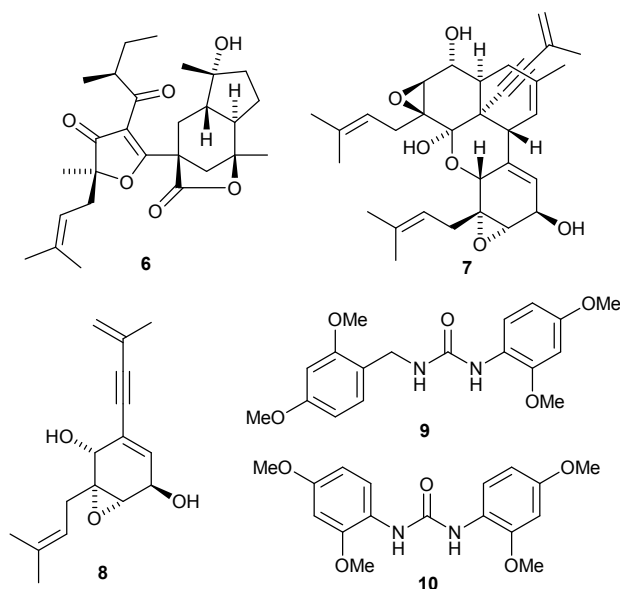
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as furanmonogone A from *Hypericum monogynum*.

The structure of lecanicillolide **1**, a metabolite of *Lecanicillium* sp. PR-M-3, was established by X-ray analysis.¹ A biosynthetic pathway to lecanicillolide **1**, involving two polyketide chains, has been proposed. The structure of phomone B **2**, a racemic metabolite of *Phoma* sp. YN02-P-3, was also established by X-ray analysis.² Phomone B **2** is a dimer of the co-metabolite rosellin **3**. Monascustin **4** has been isolated from *Monascus purpureus* fermented rice.³ It has been proposed that monascustin **4** is formed from lysine and acetoacetate precursors. Dahurelmusin A **5**, from *Elymus dahuricus* infected by *Epichloë bromicola*, is also a hybrid peptide-polyketide.⁴ The structures of monascustin **4** and dahurelmusin A **5** were confirmed by X-ray analyses.



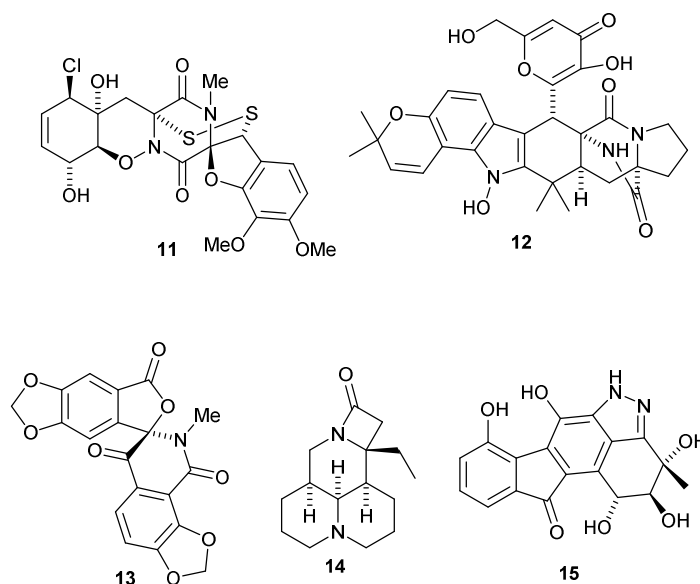


The rearranged prenylated acylphloroglucinol furanmonogone A **6** has been isolated from flowers of *Hypericum monogynum*.⁵ A biosynthetic pathway to furanmonogone A **6** has been proposed involving an oxidative cleavage of the phloroglucinol ring. The fungus *Biscogniauxia* sp. 71-10-1-1, isolated from the lichen *Usnea mutabilis*, produces several metabolites including dimericbiscognienyne A **7** and its monomeric precursor biscognienyne B **8**.⁶ Possible biosynthetic pathways to these metabolites have been presented. Pygmanilines A **9** and B **10** have been identified in the lichen *Lichina pygmaea*.⁷ The structures of these unusual aryl urea derivatives were confirmed by synthesis.



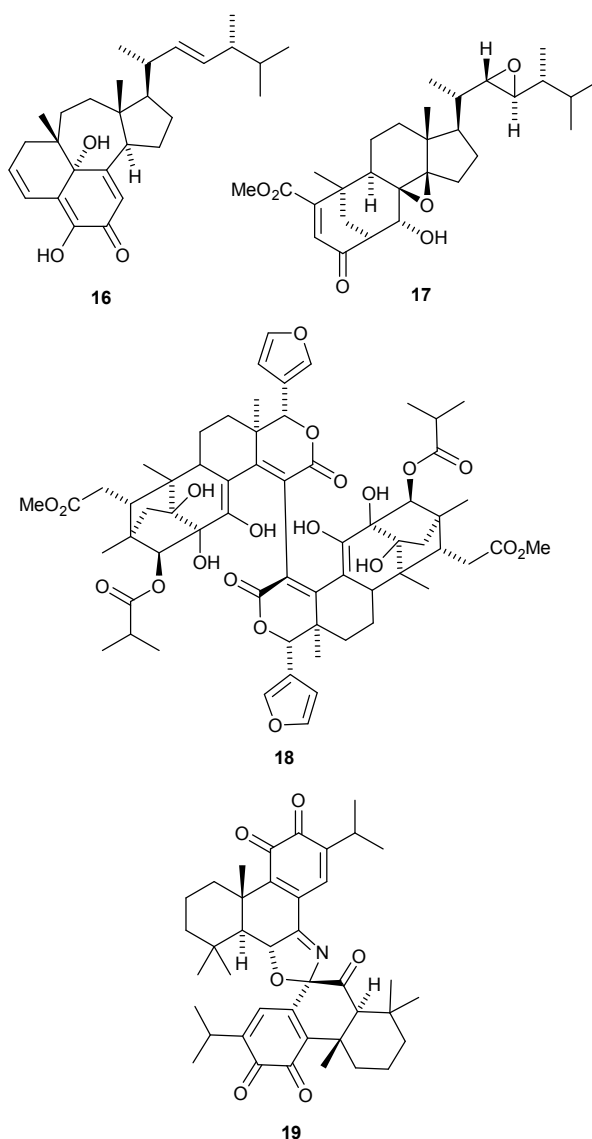
Penicisulfuranols A-F (e.g. A **11**) are unusual epipolythiodioxopiperazine alkaloids, from *Penicillium janthinellum*, that have sulfur atoms on α - and β -positions of the amino acid residues rather than both on α -carbons.⁸ Several highly modified dioxopiperazine alkaloids, including versicoamide F **12**, have been isolated from

Aspergillus tennesseensis.⁹ The structure of versicoamide F **12** was confirmed by X-ray analysis and biosynthetic pathways to this group of metabolites have been proposed. The novel spiro framework of macleayine **13**, from *Macleaya cordata*, is proposed to be formed by cleavage of a protoberberine alkaloid precursor.¹⁰ It is suggested that the β -lactam ring of sophaline A **14**, from seeds of *Sophora alopecuroides*, is formed by ring contraction of matrine.¹¹ Pyrazolofluostatin A **15**, a metabolite of marine-derived *Micromonospora rosaria*, contains an unusual pyrazole ring.¹² The structures of both sophaline A **14** and pyrazolofluostatin A **15** were confirmed by X-ray analyses.



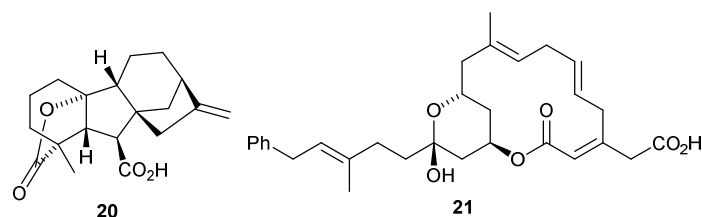
Ganotheaecolin A **16**, from the fruiting bodies of *Ganoderma theaeacolum*, has a novel rearranged ergostane skeleton.¹³ Phomopsterone A **17**, a metabolite of *Phomopsis* sp. TJ507A, whose structure was confirmed by X-ray analysis, also has a novel rearranged ergostane skeleton.¹⁴ Biosynthetic pathways to both ganotheaecolin A **16** and phomopsterone A **17** have been proposed. The limonoid dimer krishnadimer A **18**, from *Xylocarpus moluccensis*, shows non-biaryl axial chirality.¹⁵ The structure of krishnadimer A **18**, including its *P* axial chirality, was established by X-ray analysis. A crystal structure was also used to confirm the structure of the dimeric abietane

diterpenoid taxodikaloid A **19** from seeds of *Taxodium ascendens*.¹⁶ Taxodikaloid A **19** has an oxazoline ring linking to two monomers.

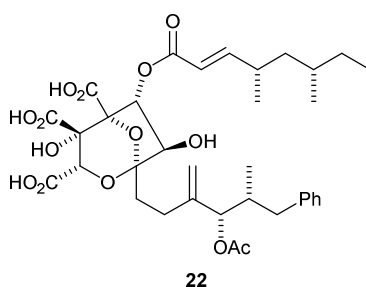


A combination of heterologous expression and knockout bacteroid incubations has allowed the elucidation of genes associated with the bacterial biosynthesis of gibberellin A₉ **20**.¹⁷ Assignment of the function of these genes has revealed that bacterial gibberellin biosynthesis is distinct to that found in plants and fungi. The characterisation of the biosynthetic gene cluster of ripostatin A **21**, a polyketide antibiotic that inhibits RNA polymerase has been reported.¹⁸ This has led to an understanding of the origin of the phenyl acetic acid starter unit of ripostatin

biosynthesis and its formation from phenylpyruvate *via* a one-carbon atom loss mediated by a phenylpyruvate dehydrogenase complex.

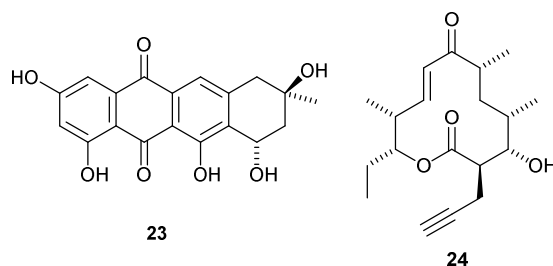


The stereochemical course of the squalestatin tetraketide synthase (SQTKS) dehydratase (DH) domain involved in the formation of the C₁₀ side-chain of squalestatin S1 **22** has been described.¹⁹ Incubation of the DH domain with six potential diketide substrates showed that only (3*R*)-3-hydroxybutyryl and (2*R*,3*R*)-2-methyl-3-hydroxybutyryl *N*-acetyl cysteamine thioesters were substrates and thus, demonstrates similar stereochemical preference as vertebrate fatty acid synthases. Further work in understanding the enzymes associated with the biosynthesis of the squalestatin S1 C₁₀ side-chain has shown that the *cis*-acting enol reductase (ER) has broad substrate scope for diketides and triketides.²⁰ A 3D model of ER based on these results suggests that after two rounds of the SQTKS, the ER sequesters its final substrate to prevent further chain extension.

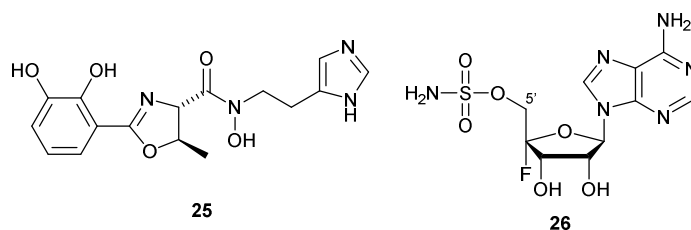


The one-pot synthesis of presteffimycinone **23**, a biosynthetic intermediate of the anthracycline antibiotic steffimycin has been achieved through the combination of eight polyketide synthase enzymes and cyclases from three different type II polyketide synthase pathways.²¹ Engineered acyltransferase domains from 6-

deoxyerythronolide B biosynthesis, that have inverted extender unit specificity has been identified by direct screening of mutants from active site saturation libraries.²² This approach led to the discovery of a set of mutants with dramatically altered selectivity, including a Tyr189Arg mutant that had preference for a non-natural alkyne-derived extender unit leading to the highly selective formation of **24**.

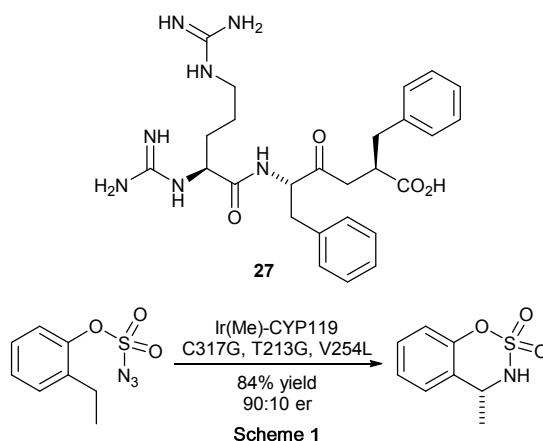


The structural elements that allow acinetobactin **25** to act as siderophore for the human pathogen *Acinetobacter baumannii* has been determined.²³ The binding and cellular delivery of Fe(III) by acinetobactin and various analogues was evaluated and revealed that the hydroxamate moiety is essential for recognition by uptake machineries, while the imidazole unit may be a promising site for antibiotic conjugation. Feeding studies with deuterium and carbon-13 labelled glycerols have provided the first biosynthetic data of the antibiotic nucleocidin **26** in *Streptomyces calvus*.²⁴ The presence of only a single deuterium atom from [²H₅]- and (*R*)-[²H₅]-glycerol at the C-5' of nucleocidin suggests that oxidation of this position occurs after ribose ring assembly and before or during introduction of the fluorine atom.



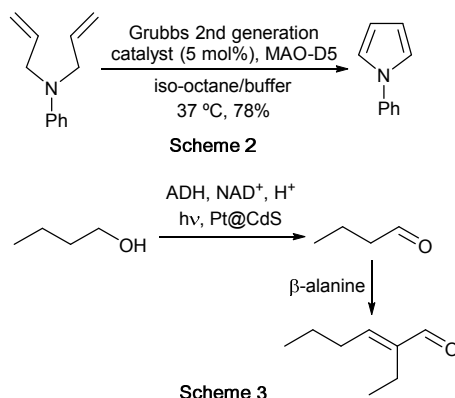
Functional characterisation of the biosynthetic pathway of ketomemcins (e.g. ketomemcin B3 **27**), carbonylmethylene-containing pseudotriptides has been

reported.²⁵ Malonyl-CoA and phenylpyruvate were found to be starter units and are combined using an aldolase dehydratase. A PLP-dependent glycine-C-acetyltransferase then mediates a Claisen-type condensation between L-phenylalanine and benzylfumaryl-CoA, forming the pseudodipeptide unit. Mutants of a thermally stable cytochrome P450 enzyme (CYP119) from *Sulfolobus solfataricus* that contain an iridium porphyrin cofactor, can catalyse enantioselective intramolecular C-H bond amination of sulfonyl azides.²⁶ The reactions proceed with high chemoselectivity of nitrene insertion into C-H bonds over reduction of the azides, forming enantioenriched sultams in high yields (Scheme 1).

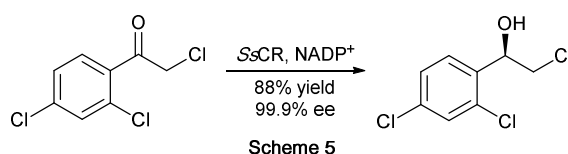
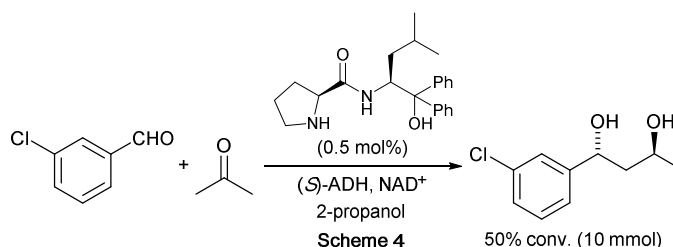


A one-pot sustainable synthesis of pyrroles from diallylamines has been achieved using a chemoenzymatic metathesis-aromatisation cascade process.²⁷ Ring closing metathesis of the diallylamines using Grubbs 2nd generation catalyst gave 3-pyrrolines that were then converted to the pyrroles in good yields by a monoamine oxidase enzyme mediated oxidation-aromatisation reaction (Scheme 2). A solar energy driven enzyme-, photo- and organo-catalytic process has been used to convert butanol to 2-ethylhexenal.²⁸ Alcohol dehydrogenase (ADH) initially converted the butanol to butraldehyde, with a platinum-seeded cadmium sulfide photocatalyst (Pt@CdS) used to regenerate the NAD⁺ cofactor (Scheme 3). To preserve enzyme and photocatalyst

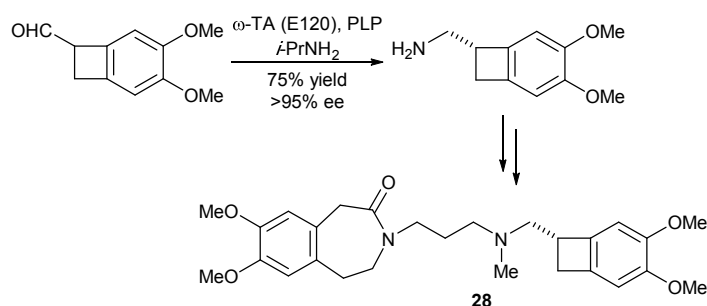
stability, a β -alanine catalysed aldol condensation under mild aqueous conditions was then used for production of 2-ethylhexenal.



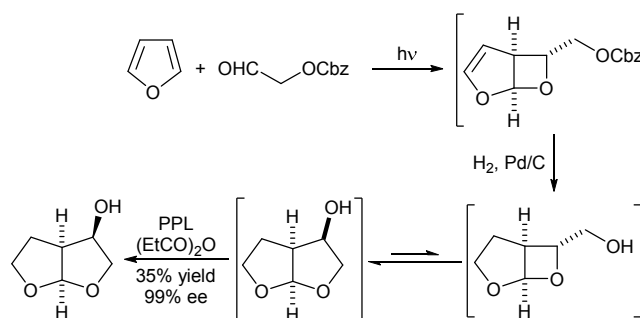
A one-pot tandem, asymmetric process that combines organo- and chemoenzymatic reactions has been developed for the enantioselective and diastereoselective synthesis of 1,3-diols.²⁹ Conditions were optimised for the organocatalytic aldol reaction and alcohol dehydrogenase mediated ketone reduction that suppressed side-reactions, allowing elevated scale synthesis of the (1*R*,3*S*)-diol from 3-chlorobenzaldehyde (Scheme 4). Enzyme screening has identified a ketoreductase clone from *Scheffersomyces stipitis* CBS 6045 (*Ss*CR) that can catalyse the asymmetric reduction of aromatic ketones.³⁰ The transformation was compatible to scale-up, resulting in a highly efficient synthesis of (*R*)-2-chloro-1-(2,4-dichlorophenyl)ethanol, a key synthetic intermediate for the preparation of various antifungal agents (Scheme 5).



Various chemoenzymatic transformations have been evaluated for the asymmetric synthesis of the heart-rate reducing agent ivabradine **28**.³¹ For example, the use of dynamic kinetic resolution of a racemic aldehyde precursor by asymmetric bioamination allowed the high yielding synthesis of the corresponding amine with excellent enantiopurity (Scheme 6). This was converted to ivabradine in a four-step sequence, in 50% overall yield and without the need of chromatographic purification. A one-pot, three-step asymmetric synthesis of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol, a key synthetic intermediate of various HIV protease inhibitors, including the drug darunavir has been developed using furan and a protected glycol aldehyde as starting materials.³² A [2+2]-photocycloaddition was followed by hydrogenation to give the deprotected oxetane (Scheme 7). Spontaneous rearrangement under thermodynamic control and kinetic resolution of the resulting racemic furanol with a lipase gave the key building block in high yield and excellent enantioselectivity.



Scheme 6



Scheme 7

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